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PRINCIPAL INVESTIGATOR: Jennifer Harvey

CONTRACTING ORGANIZATION: The Rector and Visitors of the University of Virginia
Charlottesville, VA 22904-4195

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E-Mail: jah7w@virginiaedu	

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14. ABSTRACT
Purpose: Development and validation of a personalized breast cancer risk assessment model that includes automated measurement of breast density. Scope: Assemble a cohort of women with known breast cancer risk factors and digital mammogram files for women diagnosed with breast cancer using existing data sources and match them to controls (Harvey/Knaus). Validate and refine automated breast density software (Yaffe/Harvey). Build and validate the initial comprehensive model (Knaus/Yaffe/Harvey). Major Findings: During this first year, we have established messaging, IRB and CDMRP approval, and recruitment for this study. We have recruited over 1000 of our target 4000 women cohort. We have performed outlier correction for automated measurement of breast density, including two volumetric methods (CumulusV, Volpara), developed an automated area based

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BC100474: Building a Better Model: A Personalized Breast Cancer Risk Model Incorporating Breast Density to Stratify Risk and Improve Application of Resources

INTRODUCTION:

This project is aimed at meeting informational needs by moving the nation from guidelines based on population averages to recommendations based on an individual's risk beginning with personalized mammography screening decisions. This will be done by increasing the ability to predict a women's risk of developing breast cancer by adding a strong risk factor—breast density—to current risk-assessment equations or algorithms. Our plan is, over three years, to build and initially validate a comprehensive breast cancer risk model. The overall work will require the recruitment of 1000 cases (breast cancer patients) and 3000 controls (non-breast cancer patients) from whom we will collect extensive risk factor information and breast density based on digital mammograms previously obtained at UVa. Breast cancer risk information is largely already available for cases though patients will be requested to validate and complete data. The recruitment of 3000 control patients will require engagement with the community through appropriate messaging and marketing. The measurement of breast density using automated methods will be optimized during this study through the evaluation of outlier correction, comparison of several different software methods, precision measurement, and evaluation of variation by mammography machine vendor. Once the model is complete, tested nationally, and proven accurate, it will be available for widespread use within five to six years.

BODY:

Research accomplishments are listed by Task.

Task 1: Develop procedures for team communication and coordination (month 1)
Completed. A listserve was developed for the group early on. Bi-weekly conference calls are held on Tuesdays at noon. An agenda precedes the call by at least one day. Quarterly Team meetings have been held at UVa (12 Dec 2011, 16 March 2012, 05 June 2011, planned 4 Dec 2012). Bi-annual team meetings have been held, alternating at UVa (09Sept 2011, 24 Sep 2012) and Toronto (20 April 2012, planned 03 May 2012). All PIs, advocates, and key personnel attended these meetings.

Task 2: Submit protocol to Institutional Review Board/Human Investigation Committee (months 1-3)
Completed. Study protocol, consent, and recruitment materials were drafted, submitted to UVa IRB and to DoD for review. All have been approved. The UVa IRB reviews all open protocols and consent forms annually; once approval has been received locally (anticipated in early November), the updated documents will be sent to DoD for their review and approval.

Task 3: Establish secure database (months 1-2)

Completed. A secure database has been established behind a secure firewall. The database is HIPAA compliant. Data fields and dictionary were defined. Minor changes have been made to clarify choices as the survey has gotten underway. Data linkages have been validated. Data has been successfully extracted with a small number of unanswered items. These primarily relate to details about breast cancer diagnosis (histologic type, grade, etc.). These data will be entered using our Breast Cancer Database and Clinical Data Repository in an ongoing fashion.

Task 4: Perform outlier correction for 3D Cumulus (CumulusV) (months 2-6)
The first round of outlier correction has been completed. A second retesting round will begin shortly. Cumulus V was used to analyze a set of 260 mammograms for volumetric density, and those results were compared with estimations of area density made by Dr. Harvey using our two-dimensional Cumulus 104 area method. During a work visit to Toronto from October 29 to November 3, 2011 Dr. Harvey evaluated any discordant readings using color maps to visually correlate the density map with the mammographic image.. In January 2012, Olivier Alonzo-Proulx performed the calibration of the seven mammography units of UVA, including three units at the Breast Care Center, three units at the Northridge site including the mobile clinic and one system at Orange Medical Center. Both the detectors and the thickness readout mechanisms were characterized on each of the units in order to make retrospective and prospective volumetric breast density measurements.

Further modifications were made to the density algorithm and the images were reevaluated. The new data were reviewed during Dr. Harvey's visit to Toronto (16 Apr to 20 Apr 2012). Some results are shown in Figure 1 and demonstrate an improved correlation between the gold standard Cumulus 104 and CumulusV. Correlations were also made using Volpara, a commercially available volumetric density measurement tool. Some results are shown in Figure 2 where the correlation between the two algorithms is seen to be quite high. The Volpara measurement systematically indicates lower volume, since it excludes the contribution of skin.
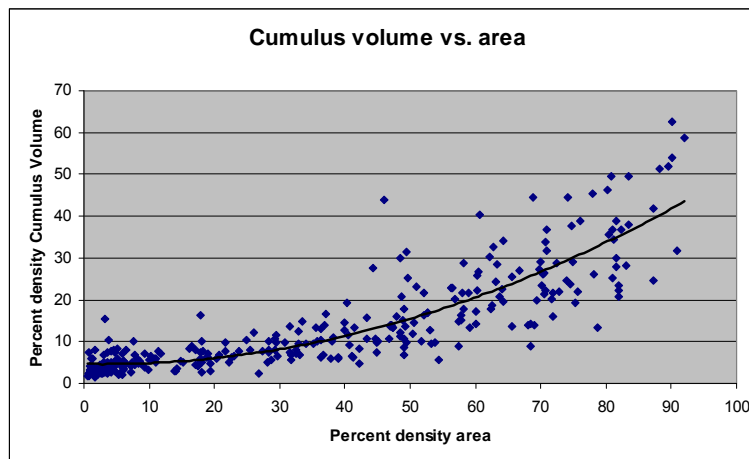

Figure 1: Cumulus 104 area (measured by Dr. Harvey) density vs. Cumulus V volume. The quadratic correlation is R= 0.87.
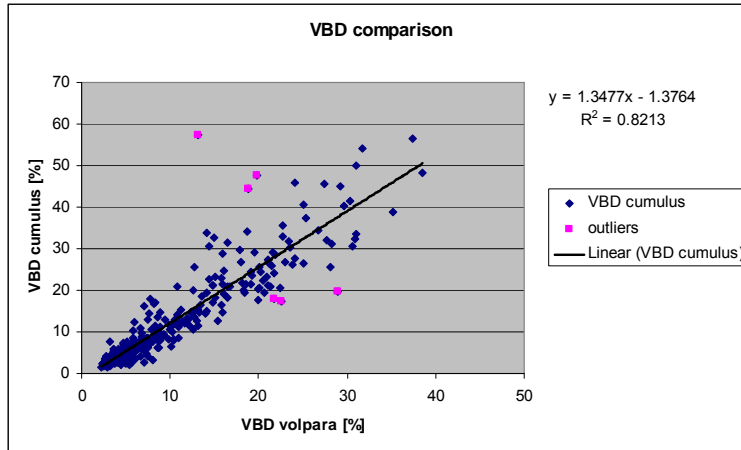
Figure 2: Cumulus volume vs. Volpara volume

A limitation of the above dataset is the fact that the mammograms were acquired over a long period of time, during which the machines may have been serviced or altered. Several detectors have been replaced since those images were obtained and this may have resulted in the calibration not representing the actual state of the imaging system at the time that the mammograms were acquired. To test CumulusV using more recent mammograms, a new dataset is being collected that will be reviewed during Dr. Harvey's next visit to Toronto beginning 29 October, 2012. The dataset will include 100 images from a GE unit and 100 images from a Hologic unit.

In order to determine whether the density measurements of mammograms performed on machines from different vendors have significantly different results, and if a "machine type" variable is necessary in the model to control for the variability, a preliminary analysis comparing the density measurements from 5 women who had mammograms taken on GE and Hologic machines one year apart was performed (Figure 3). Results indicate a fair correspondence between the two measurements, but it will be necessary to analyze a much larger number of cases, with an equal number of initial images being from each machine type. This can be done in a retrospective manner and will be addressed using the above new dataset.
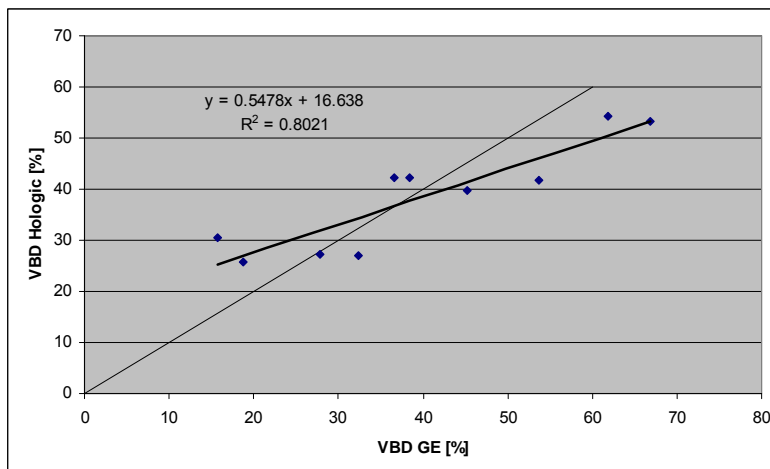
Figure 3: comparison between the volume density of the same women (left and right breasts) measured on images from GE and Hologic machines one year apart,

Task 5: Populate and validate database with existing data (months 3-6; may need to be adjusted based on IRB approval date) HARVEY

5a. Link existing radiology data sets with Clinical Data Repository (month 3-4). Our current breast cancer database is Microsoft Access format. The entries, while clear to us, are variable in style. For example, the term half-sister may have been entered as "half-sister," "half sister," or "1/2 sister." These variables reduce the accuracy of prepopulation of our database very challenging and with many errors. Because of this, we will use the database to obtain information about our case patients prior to their arrival to clinic that can be used to help patients complete the form. In addition, information that is missing or answered "I don't know" will be completed using the existing database (many patients do not know specific details about their breast cancer).

5b. Identify missing data that can be obtained via chart review (month 3-4). This will be an ongoing process as cancer case patients complete their survey. For case patients that are no longer in the area or have passed away, we will populate the information using both the MS Access database and chart review.

5c. Conduct chart review for selected cases (month 4-6). Comparison of information from the Breast Cancer Database and medical records showed good consistency (for example, details of treatment for cancer cases were the same between sources). Both sources will be used to help fill in missing data prospectively.

Task 6: Case ascertainment (month 6) KNAUS

6a. Apply inclusion/exclusion criteria to populated database (month 6).
6b. Date of diagnosis and age identification for matching with controls (month 6).
6c. Identify specific missing data fields that can be obtained by interview (month 6).

Completed. Case ascertainment was performed using a combination of our Clinical Data Repository and our MS Access Database. Over 2000 eligible cases were identified.

Task 7: Control ascertainment (month 7) KNAUS

7a. Apply inclusion/exclusion criteria to potential controls (month 7)
7b. Match to cases within five years of diagnosis of breast cancer (month 7).
7c. Identify up to 15 potential controls for each case (month 7

Control ascertainment has likewise been completed. Over 28,000 potential control patients have been identified. The cases and potential controls are contained in a MS Excel spreadsheet so that when a patient presents to the clinic, the research staff can easily see if she qualifies for the study.

Task 8: Develop Automated 2D Cumulus program (months 7-12) YAFFE

8a. Create a volumetric composition map using 3D Cumulus on Dr. Harvey's previously validated 340 mammogram dataset (months 7-9)
8b. Perform quasi-2D density analysis on dataset maps (month 10).

8c. Optimize algorithm during Dr. Harvey's visit to Toronto (month 11)

The current 2D method of Cumulus has a well validated association with breast cancer risk. However this method is labor intensive and used only in research. Because 2D methods of measuring breast density are not dependent upon having accurate measurements of breast thickness, an automated 2D Cumulus measurement may prove more reliable than 3D methods. Dr. Yaffe's group has developed an automated 2D method. Figure 4 shows the automated 2D (area) results on the same dataset presented in Task 4 (figures 1 and 2). The same limitation, the age of the mammograms, applies here. The correlation between the automatic area and the cumulus area is similar to that seen in Figure 1. However, the relation between the area measurements is linear, compared to the quadratic relation between Cumulus volume and Cumulus area. The value of R = .88 is actually better than is found in tests of inter-observer variability with well trained readers.
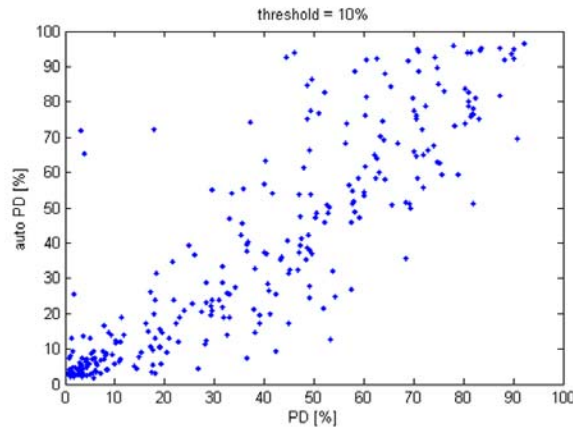

Figure 4: comparison between the PD (percent density using Cumulus area) and the automatic PD. The correlation is R=0.88 and the linear least square fit between the two PD measurements is y=0.97x+2.2%,

Task 9: Evaluate precision of 3D Cumulus method (months 7-12) HARVEY
9a. Develop IRB protocol and obtain approval (months 7-8)

Our current priority is development of a new mammogram dataset for outlier correction and comparison by manufacturer (see Task 4 above). We will work on the Precision study later this fall, after the new dataset is collected.

Task 10: Case enrollment (months 7-24) KNAUS
Task 11: Control enrollment (months 8-24) HARVEY

After building the dataset, iPads were programmed for survey data acquisition by the patient. This has been a very efficient, secure system to administer the survey. The data is uploaded to the secure server immediately, and the data is removed from the iPad after completion. A token system has been set up for patient anonymity. Patients can also access the survey from home using their token.

Case and control enrollment is well underway at two UVA sites with approximately 73 enrollments per week. As of October 11, 2012, 1081 women have been recruited and have completed the survey (245 cases and 835 controls). Recruitment is on-target; our goal was to recruit 4000 women over 18 months, which is 50 patients per week. Although the initiation and initial recruitment was slow, we have made up ground and should complete recruitment on time.

As part of the study, we are also requesting the optional donation of a blood sample from patients. The blood sample process was set up after recruitment was underway. We have obtained 259 blood samples (58 cases, 201 controls) as of October 12, 2012. These banked samples will be stored in a -80 degree Celsius freezer and available for later studies. These may be helpful if serum hormone levels are needed to further refine the model.

Task 14: Community engagement and publicity campaign (months 1-24) HARVEY
During the first few months of the study, we conducted two focus groups, which were very helpful. The project title is: The UVa Mammography Project: Shaping the Future of Breast Cancer Screening. Our advocates were invaluable in this process.

We created a project website (http://www.healthsystem.virginia.edu/pub/ct/ct15885, live date July 2012). We will not be using Twitter.

Our plan was to create a project Facebook page. However, in discussion with marketing and our advocates, the amount of anticipated traffic was small. We expanded the idea of the Facebook page to the UVa Breast Care Program. Our programmer is employed part-time by our grant with the remainder of his time funded through the Department of Radiology; this is ideal. The "go live" date for the Facebook page was August 22. The FB address has been added to our rack card. As of October 24, we have made 31 posts and the page has 85 "Likes." We are buying targeted ads for a low fee from Facebook.

A rack card and letter to potential case/control patients was developed last spring. We are very grateful to our advocates and focus groups for their hard work on these items.

We had a tent on Saturday mornings 7-9 a.m. for the Charlottesville Women's Four Miler Training Program in June, July, and August. Rack cards were distributed to the 3500 participants of the Charlottesville Women's Four Miler participants.

Our recruitment has reached a reasonable rate by recruiting women presenting to our clinics. We have not yet used advertising to bring in patients. We do anticipate that recruitment may fall of as we approach the one- year mark when there will be fewer women that are eligible. If recruitment declines, we will then send letters and do newspaper advertisements. In addition, we will monitor our recruitment regarding race/ethnicity. If control demographics are not similar to the case population, we will do targeted recruitment.

We had a local television interview regarding the project in December. Vernal Branch,

one of our advocates, generously included a piece about the project in the Virginia Breast Cancer Foundation newsletter. A piece has also gone to Albemarle Magazine- a popular local publication. We were in a short production by Ivanhoe Broadcasting about the project. This will be shown in various markets around the country.

Task 15: Conduct focus groups (months 12-20) HARVEY

The Staff of the Center for Survey Research (CSR) conducted two focus groups in January 2012. The results were very enlightening. The purpose was :

1. To understand what participants know about breast cancer screening and risk
2. To explore participants' reactions to information about breast density as a risk factor
3. To discuss the Harvey study and motivations for recruiting participants in the study
4. To discuss names for the study

The two focus groups were women without a personal history of breast cancer and women who were breast cancer survivors. The Non-Cancer Group met on January 17, 2012. Eleven participants were recruited who are patients of Dr. Harvey at the Northridge Office or referrals from the UVa Medical staff. The Survivors Group met on January 24, 2012. Nine participants were recruited who are members of a cancer support group coordinated by Diana Cole, at the Emily Couric Clinical Cancer Center, or referrals from Breast Surgery.

Agenda for the Focus Groups:

1. Discussed screening and how participants make decisions about screening
2. Kathy Repich presented Dr. Harvey's slides on risk factors and the existing models for measuring risk
3. Discussed participants' reactions to the presentation and their knowledge of the risk factors
4. Discussed recruitment for the study and what would motivate people to participate in the study
5. Presented ideas for naming the project and gave participants an opportunity to rate them and share others

The non-cancer focus group cited the following as motivating factors for participation in the study: convenience, legitimacy, importance, size of the study, self-education, learn about risk factor models, and altruism ("To help my daughter"). Cancer survivors cited the following as additional motivating factors for participation: to reduce false positives for others, altruism ("I had treatment options because of other trial participants") and "the idea that someday, there may be customized recommendations."

The results of the focus groups lead us to these considerations for messaging on

recruitment materials: highlight convenience of participation, address patient privacy, highlight size / scope / potential impact of the study, assess effectiveness of giveaways as recruitment tool – non-cancer group not in favor public display of study participation, and altruism ("Your participation could impact future generations."). We subsequently decided not to give away study logo items (t-shirts, tote bags), but to thank participants with a thank you note highlighting their altruism. The note also includes a $5 gas card as a token of appreciation.

KEY RESEARCH ACCOMPLISHMENTS:

- Obtained IRB and CDMRP approval for study
- Established a secure database
- Established data elements for survey and set up iPads as survey instruments
- Identified over 2,000 potential cases and over 28,000 controls
- Initiated study enrollment. As of October 11, 2012, 1081 women have been recruited and have completed the survey (245 cases and 835 controls). Of these patients, 259 have submitted blood samples (optional) (58 cases, 201 controls).
- Performed outlier correction for area versus CumulusV and Volpara density measurement software programs. The quadratic correlation with manual area density measurement for corrected CumulusV is R= 0.87.
- Developed Automated Cumulus2D software program and compared with manual area density measurements; R=0.88.
- Conducted two focus groups with the help of our advocates and the Center for Survey Research. This formed our messaging for naming the study and recruitment materials.
- Engaged community through the Charlottesville Women's Four Miler Race and Training Program, a study website (http://www.healthsystem.virginia.edu/pub/ct/ct15885), and FaceBook page (UVa Breast Care Program, 85 Likes, 35 posts)

REPORTABLE OUTCOMES:
- A process for specimen handling has been established for women donating a blood sample. The samples are divided into 20 serum aliquots and buffy coat for DNA.
- Grant from the Charlottesville Women's Four Miler, $2400, May 2012, for iPads (survey instrument)
- Grant from the Charlottesville Women's Four Miler, "Breast Cancer Plasma and DNA Bank: use for development of integrative breast cancer risk prediction method. " $77,733, September 2012. Funds to freeze and store blood samples obtained through this project.

CONCLUSION:
We have completed the vast majority of tasks designated for our first year. We conducted two focus groups with our advocates that developed messaging for the study. We have engaged our community so that women are receptive to our request for study participation. We have a successful recruitment method and should be on target to complete recruitment by the end of year 2. Our secure server and dataset have been set up and validated. Our automated volumetric density measurement methods show very good correlation with the gold standard manual area based method. We developed an automated area based density measurement program as well, which also shows very good correlation with the gold standard manual method. Over the next year, we will continue to refine our density measurements so that they are ready for incorporation into our Better Breast Cancer Risk Assessment Model.

REFERENCES:
None

APPENDICES:
None